

# DEADLY OVERCAUTION: FDA'S DRUG APPROVAL PROCESS

by Sam Kazman

When the federal Food and Drug Administration announces its approval of an important new drug, the event is invariably portrayed as an administrative achievement. This has always puzzled me. It seems that a question hangs over these announcements that almost always goes unasked, though I understand why FDA might not care to answer it. The question is this: If a drug that has just been approved by FDA will start saving lives tomorrow, then how many people died yesterday waiting for the agency to act?

By "yesterday" I do not just mean the day before; I mean the two to three years that it generally takes FDA to approve a New Drug Application (NDA). Under federal law, no new drug can be marketed in this country until FDA approves it as safe and effective. FDA makes its finding on the basis of the manufacturer's NDA, which may contain over 100,000 pages of data from clinical tests that took from two to ten years to complete. During all this time the drug is unavailable to physicians and the public, except on a very limited basis as part of some clinical trial.

FDA, of course, is not the cause of all clinical testing; much of it is a necessary part of drug development and would occur even in the absence of FDA regulation. But it is clear that these regulations have made the development of new drugs significantly more expensive and time-consuming. Studies indicate that FDA's requirements have more than doubled development costs

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for approved drugs and have substantially reduced the rate at which new drugs are introduced, creating a large lag in the availability of new drugs in this country as measured against comparable foreign countries.<sup>1</sup>

While FDA's defenders dispute the magnitude of these impacts, their essential argument is that these effects are far outweighed by the protection that FDA provides against unsafe and ineffective drugs. Their arguments inevitably go back to the event that led to the present day FDA and that is paradigmatic in any discussion of drug regulatory policy—thalidomide.

#### **THALIDOMIDE AND THE EXPANSION OF FDA**

Thalidomide was introduced in Germany in 1957 as a sedative distinguished by its nontoxicity. It was eventually sold in over 40 countries before its link to severe birth defects became apparent. In the United States approval for thalidomide, requested in 1960, was withheld by its FDA reviewer, Dr. Frances Kelsey, while she investigated reports that the drug caused peripheral nerve damage. In 1961 news of thalidomide's fetal effects led to the drug's withdrawal from the world market. Because of Dr. Kelsey's actions the drug was never sold in this country, and the US was largely spared the thousands of birth defects that occurred abroad. Dr. Kelsey received the President's Gold Medal for Distinguished Service for her work.

The thalidomide catastrophe was the catalyst for a major expansion of FDA's powers in 1962 under the Kefauver-Harris amendments to the Food, Drug and Cosmetic Act. The earlier statute, enacted in 1938, had prohibited the marketing of new drugs until they were found to be safe by FDA. The 1962 amendments added a new requirement—drugs would now have to be found to be both safe and effective before they could be introduced. This was ironic, because the threat posed by thalidomide was one of safety, not efficacy, and FDA's review powers under the 1938 act had succeeded in barring it from the American market.

The 1962 amendments also gave FDA far greater power over human testing of new drugs. Clinical trials of new drugs are generally performed in three stages: Phase

1 tests are aimed at obtaining basic data on drug toxicity and side effects, and are usually conducted on a small number of healthy subjects (usually under 100). Phase 2 tests study effectiveness as well as side effects, and generally involve several hundred subjects divided into treatment and control groups. Phase 3 testing examines more detailed issues such as optimal dosage and involves hundreds to thousands of subjects over multi-year periods.

Under the 1962 amendments all clinical (i.e., human) testing of new drugs, and of previously approved drugs being studied for new uses, must be cleared in advance by FDA under its investigational new drug (IND) procedures. FDA approval of an IND application to begin clinically testing a new drug hinges on such factors as the adequacy of pre-clinical (animal) testing, the details of the proposed test plan and the risk to which human participants will be subjected. Even after they are underway, approved tests can be halted if FDA subsequently becomes dissatisfied with them.

FDA's powers were expanded in other ways as well. Under the 1938 act NDAs were automatically approved unless the agency denied them. Under the new law it is disapproval that is automatic; for an NDA to be approved FDA now has to make an affirmative finding of safety and efficacy. Moreover, the claims that a manufacturer can make for a drug are limited to those approved by the agency for the drug's label.

The 1962 amendments fundamentally changed the nature of both the agency and the drug development process. "FDA shifted after 1962 from essentially an evaluator of evidence and research findings at the end of the R and D process to an active participant in the process itself,"<sup>2</sup> producing a transfer of "primary decision-making authority in pharmaceuticals from market mechanisms to a centralized regulatory authority."<sup>3</sup>

### **MORE GOVERNMENT, FEWER NEW DRUGS**

While the 1962 amendments were aimed at protecting public health, it gradually became evident that they were seriously restricting pharmaceutical innovation in this country. Between 1962 and 1967 the average review time for an NDA more than tripled, rising from seven



months to thirty months.<sup>4</sup> Despite numerous claims of FDA streamlining in recent years, average NDA review time has not improved, and ended the 1980's at over 32 months per application.<sup>5</sup>

The higher standards for NDA approval under the new law led to an increase in manufacturers' pre-NDA investigational work as well. The total development time for a new drug, which averaged from 4 to 6 years in the early 1960's, has now doubled to ten years.<sup>6</sup> (See Chart 1, page 39.)

Development time is not the only factor that has worsened. The number of new drugs under development in the US declined as well. From 1975 to 1979 the number of new domestically developed drugs that entered human testing for the first time dropped to half the rate for the preceding decade. According to one study of this decline

the most common explanation given by the industry people was that severe scientific and political pressures were exerted in the mid-1970s on the industry's pre-clinical research. The increased FDA requirements were for more tests...and, perhaps more importantly, for large increases in the detail, standards, and documentation of the testing...One industry manager said that the simultaneous increase in...standards and attacks on particular drugs caused many industrial laboratories to virtually cease research on new drugs and to divert their resources into auditing their old data instead of working on new INDs...<sup>7</sup>

The most dramatic evidence of the effect of the 1962 amendments is the shift in drug innovation leadership between the US and Great Britain, which has scientific and medical standards comparable to ours. In the period immediately following the new law, before its full effects were felt, the US led Britain in new drug introduction. For the mutually available drugs (that is, drugs available in both countries) that were introduced between 1962 and 1965, the US had, on average, a six month lead in being the country of first introduction. However, from 1966 to 1971 Great Britain took the lead; on average, mutually available drugs were introduced 15 months earlier in Britain than in the US.<sup>8</sup>

Britain had a similar lead in exclusively available

# CHART 1

## Drug Development and Approval Process

### Preclinical Testing

| YEARS                        | 1                                     | 2 |
|------------------------------|---------------------------------------|---|
| Test Population              | Laboratory and Animal Studies         |   |
| PURPOSE                      | Assess safety and biological activity |   |
| % of all new drugs that pass |                                       |   |

FILE  
IND

| Phase I                     | Phase II                                       |   | Phase III  |   |   |
|-----------------------------|--|---|--|---|---|
| 3                           | 4  | 5 | 6  | 7 | 8 |
| 20 to 80 Healthy Volunteers | 100 to 300 Patient Volunteers                  |   | 1,000 to 3,000 Patient Volunteers  |   |   |
| Determine safety and dosage | Evaluate effectiveness. Look for side effects. |   | Verify effectiveness, monitor adverse reactions from long-term use.  |   |   |
|                             |  |   | Expedited Review: Phases II and III combined to shorten approval process on new medicines for serious & life-threatening diseases. |   |   |
| 70 % of INDs                | 33 % of INDs                                   |   | 27 % of INDs   |   |   |

| FILE<br>IND<br>A | FDA                                     | Approval                         |
|------------------|---|----------------------------------|
|                  | 9                                       | 10                               |
|                  | Review usually takes about 2 to 3 years | Post-marketing safety monitoring |
|                  |   | Large-scale manufacturing        |
|                  |   | Distribution                     |
|                  |   | Education                        |
|                  | 20 % of INDs                            |                                  |

It takes a decade on average for an experimental drug to travel from lab to medicine chest. Only five in 4,000 compounds screened in preclinical testing make it to human testing. One of these five tested in people is approved.

From: Pharmaceutical Manufacturers Association, *New Drug Approvals in 1989*.

drugs—that is, drugs introduced into only one of the two countries. Of the 98 drugs that became exclusively available between 1962 and 1971, 77 were introduced first in Britain.<sup>9</sup>

The most recent report on these trends shows that they have continued through the 1980s. From 1977 to 1987, 204 new drugs were introduced in the US; of these, 114 were available in Britain, with an average leadtime of more than five years per drug. On the other hand, of the 186 new drugs introduced into Britain during this period, only 41 were already available in the US and then only by an average of two and a half years. As for exclusively available drugs, there were 70 in Britain but only 54 in the US. The greatest lag times for the US were in the areas of cardiovascular, respiratory, central nervous system and cancer drugs.<sup>10</sup>

Just as alleged FDA reform has had no effect on NDA review time, it has similarly failed to reduce US drug lag. Average British leadtime in the second half of the period studied above, between 1983 and 1987, was as large as it was in the first half.

The study's authors concluded that, important drugs still become available later in the United States, some much later, than in the United Kingdom. This is true both for drugs representing important therapeutic gains, as well as for those representing modest or little gains. Moreover, the small difference in safety discontinuations in the two countries does not support the argument that delay protects the public from serious unforeseen adverse effects.<sup>11</sup>

#### THE INVISIBLE RESULTS OF INEVITABLE BEHAVIOR

There are two basic types of errors which a drug regulator can make: the first is to mistakenly approve a drug which later turns out to have serious adverse side effects; the second type of error is to mistakenly reject, or even delay in approving, a beneficial drug. From a public health standpoint, both types of errors are equally serious in nature, because both will lead to the unnecessary loss of life. Overcaution in approving a needed drug can be just as deadly as lack of caution in approving a bad drug.<sup>12</sup>

The fundamental problem at FDA is that it is

overcautious in approving new drugs. This does not stem from its budget or from staff morale or from the individuals appointed to run it; it is a problem that is inherent in the agency's political nature, which makes it a creature of congressional oversight and media pressure. The thalidomide tragedy, the source of FDA's current powers, has become the guiding model for the agency. Every new drug is potentially another thalidomide. From the FDA commissioner to the bureau heads to the individual NDA reviewers, the message is clear: if you approve a drug with unanticipated side effects, both you and the agency will face the heat of newspaper headlines, television coverage and congressional hearings.

On the other hand, if FDA insists on more and more data from a manufacturer, and finally approves a drug which should have been on the market months or years before, there is no such price to pay. Drug lag's victims and their families will hardly be complaining, because they won't know what hit them. They do not know what INDs and NDAs lie waiting for approval at FDA, nor do they follow pharmaceutical news from abroad or progress reports on clinical trials. (Unless, that is, they are sufficiently lucky, rich or politically connected to get into such a trial.) They only know that there is nothing their doctors can do for them. From the standpoint of media and politics, they are invisible.

As former FDA Commissioner Alexander Schmidt once stated,

in all of FDA's history, I am unable to find a single instance where a Congressional committee investigated the failure of FDA to approve a new drug. But, the times when hearings have been held to criticize our approval of new drugs have been so frequent that we aren't able to count them...The message to FDA staff could not be clearer. Whenever a controversy over a new drug is resolved by its approval, the Agency and the individuals involved likely will be investigated. Whenever such a drug is disapproved, no inquiry will be made. The Congressional pressure for our negative action on new drug applications is, therefore, intense. And it seems to be increasing...<sup>13</sup>

The clinical research director of a major pharmaceutical

company involved in Alzheimer's research put it more directly:

There won't be any breakthrough products out there because every time the trials run into seizure or liver enzymes, the risk will be emphasized and the benefit will be ignored.<sup>14</sup>

Similar sentiments were expressed by officials of the National Cancer Institute, who accused FDA of being "mired in a 1960s philosophy of drug development, viewing all new agents as...poisons."<sup>15</sup>

The political invisibility of drug lag's victims is the major reason for FDA's inherent overcaution in approving new drugs. Caution may sound like a good thing when it comes to public health, but there are times when overcaution can be deadlier than lack of caution, which is why we do not elaborately stress-test a rope before throwing it to a drowning man.

A stark example of FDA's skewed treatment of risks and benefits is the agency's ten year delay (from 1967 to 1976) in approving a variety of beta blockers to reduce heart attacks. FDA Commissioner Donald Kennedy defended this delay as follows:

A major reason...was the suspicion that a number of B-blockers might be tumorigenic, and the resulting (FDA) requirement that long-term animal studies be undertaken to investigate this possibility...It (now) appears that certain B-blockers are potential tumorigens...Since B-blockers (are) intended for long-term use in a great many patients, the FDA's...decision to require long-term carcinogenic-effect testing before clinical use spared patients in the US a potentially dangerous kind of exposure.<sup>16</sup>

But to Dr. William M. Wardell, a major scholar of drug regulation, this is a very minor side of the story:

The proper use of (the B-blocker) practolol...could now be saving 10,000 lives each year in the US at a cost, in terms of side effects, that can now be made trivial by comparison...These important advances are what Dr. Kennedy triumphantly takes credit for 'protecting' us from; the concept of risk avoidance has been turned pyrrhically on its head.

In addition to 'saving' the US from the only drugs that



had, up to 1977, been definitely shown to reduce postinfarction mortality, the FDA's B-blocker policy has set back cardiovascular therapy in this country by years. At a time when the frontiers of B-blocker research throughout the world had moved on to the question of preventing coronary death and reinfarction, economic, clinical, and intellectual resources of both the FDA and industry in the US went into reexamining... efficacy and toxicity... (about which the answers were already well known...); this scientific wheel-spinning lasted for approximately seven years...<sup>17</sup>

FDA's action may make little medical sense, but unfortunately it makes perfect political sense. In terms of congressional reaction and media coverage, the post-approval discovery that certain beta blockers induced tumors would have been devastating to FDA. Even a score of unanticipated deaths from a new drug are enough to set Congress off,<sup>18</sup> while the loss of several thousand lives due to a delayed approval has practically no political impact.

FDA's skewed incentives have other results as well. When the agency believes that satisfactory treatment for a certain illness is already available, new drugs for it will frequently have to pass an even higher standard of proof. Treatments thus tend to become frozen at levels that are only moderately successful—after all, why take a chance on something new when the old is adequate? (And if the new drug has some unrealized potential, who'll complain about its absence?)

The possibility of unapproved use can also become a back-door factor in the denial of an NDA. Levamisole, for example, has recently shown such great promise in treating colon cancer that FDA is permitting its distribution while clinical tests are still underway. The original levamisole NDA, however, filed in the early 1970's for its use as an anti-worm drug, was never approved by FDA. The official reason was that adequate anti-worm agents were already available. The real reason appeared to be concern that levamisole would be put to unauthorized use against cancer, since reports of the drug's immunity-boosting effects were already circulating at that time.<sup>19</sup> Thus, yet another revolutionary drug turns

out to be a breakthrough in bureaucracy rather than in medicine.

RU-486, the new French abortion pill, may meet a similar fate. Its consideration by FDA will undoubtedly be mired in the abortion debate. The drug, however, has also shown promise against brain and spinal tumors—uses which will be submerged by political opposition to its availability.

The FDA process has also created a regulatory structure which benefits certain segments of the pharmaceutical industry. Large, established firms have developed an expertise in dealing with FDA that probably accounts for a good part of their capital value; they are also able to spread the costs of FDA compliance over a large product line. For new entrants in the field, on the other hand, FDA regulation is a sizable competitive barrier.<sup>20</sup>

#### **AIDS AND THE ILLUSION OF FDA REFORM**

The major exception to drug lag's invisibility has been the AIDS crisis and the emergence of a nationwide network of AIDS activist organizations. More than any other public health issue, AIDS has highlighted the grotesque consequences of FDA policy. It has presented the spectacle of federal officials denying unapproved drugs to incurably ill people on the ground that the denial is for their own good, while AIDS victims and their supporters resort to drug smuggling in order to preserve their dignity and autonomy. The October 1988 AIDS demonstration at FDA headquarters marked the first time that the agency has been physically confronted, en masse, by its victims.

The AIDS crisis has sparked a number of minor reforms. Access to experimental drugs has been made slightly easier through such new procedures as "treatment INDs" and "parallel tracking," under which promising drugs can be used for treatment before they receive final FDA approval. FDA is allowing the limited importation of unapproved foreign drugs by individuals (though at the same time, paradoxically, these same drugs still cannot be legally obtained from domestic manufacturers). The agency has begun to accept test data on experimental drugs from community-based programs, a significant

departure from the centralized clinical trials that were previously an absolute prerequisite for FDA approval.

These changes sound impressive, but they are only the latest in a long series of agency reforms that have failed to significantly improve drug regulation. In 1975, for example, the agency began a "priority review" to speed the approval of promising new drugs. This fast-tracking has had some apparent successes—AZT, for example, the only drug yet approved for treating AIDS, went through the NDA process in a recordbreaking 107 days. Nonetheless, fast-tracking depends on FDA's alleged ability to pick winners in advance—a claim that is as ubiquitous among government planners as it is unsupported. Consider this account of FDA's 1978 approval of valproate sodium for treating epilepsy:

Although this drug was acted on with alacrity in the glare of unprecedented publicity in the final stages leading to its NDA approval...its early history is not one of speed...The IND study on this drug was submitted in December 1974, by which time the drug had been marketed abroad for several years and was already recognized as a drug of choice for certain types of epilepsy. Nevertheless, the FDA's classification system assigned it to class B (i.e., not meriting the fast-track treatment). It was not until October 1977 that the drug was first referred to the FDA's Neurologic Drug Advisory Committee. The fact that the FDA's system failed to recognize the importance of an already-marketed drug of choice does not make one sanguine about the FDA's claimed ability to identify important new drugs even earlier, i.e., at the investigational stage—before a drug's therapeutic potential can be predicted by anyone—when the research process is most susceptible to inhibitory regulation.<sup>21</sup>

Just as the AIDS crisis has not produced any fundamental reform of FDA, it has also not improved the media's understanding of the agency's role in drug development. Most FDA actions are not agency accomplishments; they are the termination of FDA restraints on *private* accomplishments. Despite countless stories on AIDS protests, drug smuggling and underground testing, however, reporters continue to get this simple fact



wrong. In early 1990, for example, FDA allowed AZT's manufacturer to halve the drug's recommended dosage, a very significant step given AZT's high cost and toxicity. The dosage cut, however, was almost universally reported as an FDA achievement, despite the fact that all the agency had done was to approve a request made by the manufacturer several months earlier.<sup>22</sup>

The recent FDA reforms, moreover, are jeopardized by new moves to tighten the drug approval process. The generic drug scandal, in which certain firms were found to have bribed FDA staffers to delay their competitors' NDAs, has created a legislative backlash to the little deregulation that FDA has accomplished. Similarly, the General Accounting Office recently reported that more than half of the drugs introduced in 1976 to 1985 had side effects that were discovered only after they had been approved.<sup>23</sup> In its demand for pre-approval omniscience, of course, GAO totally ignores the extent to which a more elaborate NDA review process would further delay new drug approval—an inexplicable approach, especially since GAO itself has criticized FDA's slowness.<sup>24</sup> GAO's new report, requested by a leading congressional advocate of stricter FDA regulation, has become another supposedly weighty argument against FDA reform.

The AIDS crisis became an exception to drug lag's invisibility because of gay political power. Had those at risk for AIDS been less organized, as is the case with victims of most critical diseases, the availability of AIDS treatments would be a fraction of its current level. This may be the way politics works, but it is not the way medicine should work.

#### **PUTTING SOME NUMBERS ON THE FACELESS**

FDA claims to assure drug safety and efficacy. Just what these qualities are, and whether government is in fact necessary for their assurance, are debatable questions. But regardless of how we ultimately answer them, we should have some handle on what FDA's drug approval regime costs us. After all, when a salesman tells you that his product is absolutely essential, it usually is not a bad idea to ask the price.

FDA's \$100 million drug review budget is the most



obvious component of this price, but it is also the most minor. The major cost is the invisible one—the therapeutic benefits of new drugs that we lose while these drugs are under review. For example:

### **Misoprostol and Gastric Ulcer Bleeding**

In December 1988, FDA announced its approval of misoprostol—the first drug to prevent the gastric ulcers that are caused by aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). These medications are frequently taken in large doses by arthritis sufferers, and the gastric ulcers which frequently result undetected from their use cause 10,000 to 20,000 deaths each year through internal bleeding and other complications. Misoprostol is reported to produce a 15-fold reduction in these gastric ulcers, and its life-saving potential led FDA to give its highest therapeutic potential rating, 1A, to the drug's NDA.<sup>25</sup>

The NDA was approved by the agency in a relatively rapid nine and a half months. Nonetheless, by the time the drug was approved in the US it was already available in 43 foreign countries, in some of them since 1985.

In a press release accompanying the misoprostol approval, FDA Commissioner Frank Young stated, "This drug should save lives as well as costly hospitalizations." Thus, the question with which this article began—if a new drug will save lives after its approval, then how many lives were lost while it was being reviewed?

This is but one aspect of the drug lag that has been discussed above. It does not measure FDA's burden on pre-NDA development time. On the other hand, it avoids the complexity of international comparisons by focusing on a distinct time period during which a drug's unavailability is clearly FDA's doing—the period that begins with the filing of an NDA and ends with its approval.

Moreover, this approach is similar to that taken by many federal agencies in publicizing the hazards of toxic substances and other health perils. Why not treat the hazards of FDA regulation in the same way?

The calculation for misoprostol would be as follows. If the drug is, as reported, 94 percent effective and if, as

FDA estimates, there are 10,000 to 20,000 gastric ulcer deaths annually due to NSAID use, then misoprostol potentially could have saved 8,000 to 15,000 lives during FDA's nine and a half month review period.

This post-approval audit is admittedly inexact. Misoprostol may never reach all of those who might benefit from it, and it certainly did not achieve such widespread use in its first months on the market. On the other hand, misoprostol's marketing was on hold for the full duration of FDA's review period; whatever level of use misoprostol reaches a year from now, we can assume that same level would have been reached nine and a half months earlier were it not for this FDA review.

In short, 8,000 to 15,000 lives is a fair starting point for calculating the cost of FDA's review of misoprostol. FDA can come up with its own figures if it disputes this, but at least let it come up with *something*. Had Frank Young announced that "misoprostol will save lives, but we did lose several thousand people while FDA went over the manufacturer's paperwork," the public's perception of the agency might have undergone a rather fundamental shift.

As usual, however, the drug lag angle did not appear in coverage of the misoprostol story. Its approval was reported as a triumph of rapid administrative action. Its manufacturer, pleased with FDA's speed, was not about to antagonize the agency that controlled its livelihood. Those who might have been saved had the drug been available earlier rested in peace.

### **Thrombolytic Therapy for Heart Attacks**

Drug lag was a more prominent issue in FDA's 1987 approval of thrombolytic (clot-dissolving) therapy for heart attacks, but it was still ultimately skirted by the agency.

In November 1987, FDA approved streptokinase as the first drug which could be intravenously administered to reopen the blocked coronary arteries of heart attack victims. Streptokinase had been shown to reduce in-hospital mortality among heart attack patients by 18 percent. In the US approximately 700,000 heart attack patients are hospitalized annually, of whom 9 percent die in-hospital. Thus, streptokinase could potentially save 11,000 of these lives each year.

FDA's approval of this use for streptokinase came a full two years after its NDA was filed, which means that 22,000 deaths might have been prevented in the interim.<sup>26</sup> Even after an FDA advisory committee recommended approval of the NDA in May 1987, it still took the agency six months to issue its decision.

The streptokinase approval was overshadowed by the agency's handling of TPA, a genetically engineered thrombolytic agent that appeared to be even better than streptokinase. In 1985 the National Heart, Lung and Blood Institute (NHLBI) had abruptly halted a study comparing the two drugs because TPA appeared to be so much more effective that its researchers decided they could not ethically withhold TPA from any of their test subjects. TPA's manufacturer, Genentech, filed its NDA in April 1986.

At its May 1987, meeting however, in a decision that stunned many observers, the same FDA advisory committee that recommended approval of streptokinase voted against the TPA application. The committee was satisfied that TPA was effective in dissolving clots, but it wanted mortality data as well—that is, statistics showing that TPA-treated patients survived longer than untreated patients. Among the committee's concerns was the incidence of strokes that had occurred among some TPA patients.

In short, while the NHLBI researchers viewed TPA's unavailability to some of their trial subjects as so medically unethical as to require premature termination of their study, the FDA advisory committee recommended that the drug be withheld from the entire nation.

The advisory committee's recommendation was heavily criticized in certain quarters. The *Wall Street Journal* ran a series of articles and editorials which indicated that much of the dispute over TPA stemmed from a jurisdictional battle between two FDA bureaus, one responsible for drugs, the other for genetically engineered products. *Science*, one of the world's most respected scientific journals, editorialized that,

when a regulatory agency that licenses drugs for heart attacks stumbles, it may have not only egg on its face but blood on its hands...A drug that dissolves blood clots should no longer have to

answer whether such an action prolongs life.<sup>27</sup>

FDA did finally approve TPA shortly after it acted on the streptokinase NDA. By that time TPA was available in eight other countries, among them France, Austria, New Zealand and Germany. At his press conference announcing the approval, Commissioner Young brushed aside criticism of FDA's delay on TPA as the work of stock speculators, stating that "to be able to clean out an artery but at the same time produce a massive stroke would not be a very good result."

To eat chicken but at the same time choke to death on a bone would not be a very good result either. It is also a strawman proposition. A bad outcome is meaningless unless we can weigh the likelihood of its occurrence against the anticipated benefit of the action.

Commissioner Young went on to instruct the public on the need for speed in treating a suspected heart attack. "Don't deny the symptoms. Don't wait," he urged. "Seek the care of a physician so that you can make yourself available for this type of therapy." This recommendation was a far cry from FDA's own approach in approving the drug.<sup>28</sup>

The post-approval audit described above could be applied to any newly approved drug. By putting numbers on an otherwise invisible cost of FDA review, such an audit would bring some balance to public perception of FDA's function.

Is such an audit feasible? Commissioner Young didn't doubt it when I asked him about this in 1989: "Yes, I think the balances can be done. Have they been focused on in that way? Absolutely not."

Would FDA do such an audit? This got a different response from the Commissioner:

We think that, in part, this is something that should be studied by others. We do have a job of getting drugs that are safe and effective on the market at a time when we can hardly meet our time limits as it is, though this scholarship is very important.<sup>29</sup>

In short, don't hold your breath waiting for the agency to come out with these numbers.

On the other hand, FDA is not the only organization that could conduct a post-approval audit.



Within the federal government such agencies as the Council of Economic Advisers and the Office of Management and Budget would be well equipped to undertake such an audit, either periodically—examining all new drugs approved within a given time period—or on the occasion of major FDA drug approvals. Outside groups such as the National Academy of Sciences could perform the audit as well. What is important is that the numbers come out, so that FDA's announcements are received by something more than the uncritical applause that usually greets them.

### **ACCESS TO DRUGS—WITH FDA'S ADVICE, BUT WITHOUT ITS CONSENT**

A post-approval audit would put needed pressure on FDA, but more is needed if we are to avoid the toll of the current system. Attempts at fine-tuning the regulatory process, such as treatment INDs, may produce small temporary improvements, but they inevitably run into the brick wall of a system committed to playing it safe no matter how deadly the consequences. Moreover, FDA's safety and efficacy criteria are valued by too large a segment of the public to make their abolition politically feasible.

There is, however, a simple way to preserve FDA's criteria while eliminating the deadly costs of the current regime: change FDA's veto power over new drugs to a system of certification. Let the agency continue to review safety and efficacy, but allow unapproved drugs, clearly labelled as such, to be available by prescription.

Under this approach those patients and physicians who wish to be guided by FDA's judgments would face no obstacle whatsoever; they could simply restrict themselves, as they do now, to approved drugs. But a critically ill individual, faced with the need to go beyond this circle of official approval, could do so under the care of a physician.

This approach would bring pharmacology in line with the rest of medical care, where government approval is the exception, not the rule. FDA, after all, does not approve surgical methods, yet we do not worry about podiatrists doing in-office brain transplants. Physicians

prescribing unapproved drugs would need good reasons under malpractice law for doing so, especially if approved alternatives were available. Patients using such drugs would know they were taking a special risk; unapproved drugs would bear the regulatory equivalent of a skull-and-crossbones and would be accompanied by informed consent documentation. And if FDA approval is truly medically valuable, then the use of these drugs would be remain relatively small.

Would snake oil be sold? Would patients be conned? Would unscrupulous doctors connive with fly-by-night drug makers to sell us elixirs that were worthless or worse? Perhaps, but these inequities already occur, and there is no reason to suppose that their costs outway the advantages of such an approach. In fact their incidence might well decline as unapproved drugs moved from the medical underworld into legitimacy, just as alcohol poisonings dropped when Prohibition was repealed.<sup>30</sup> It is the current centralized decisionmaking process, with its inherent bias, that holds the potential for true catastrophe.

Drug safety is not a hard and fast concept. At the scientific level, it is often the subject of intense disputes among experts. At the level of personal values and decisions, therapeutic risks that are acceptable to one person may be out of the question for another. At neither level should this be the subject of administrative edict. Drug safety "can be meaningfully defined only in terms of individual choice, not society-wide judgments of 'safety and efficacy.'"<sup>31</sup> Government may attempt to educate us, but it has no business issuing across-the-board mandates on how we should protect our health and our lives.

We have all seen pictures of thalidomide babies, but we know nothing about the victims of FDA's 10-year delay in approving beta blockers, or of its 2-year delay on cardiac thrombolytics, or of any of the other lags that it has silently caused. This imbalance in knowledge is the driving force behind FDA's current drug approval system. That system is consistent with neither good government nor good science nor respect for individual liberty and dignity, and it is time we moved beyond it.

## ENDNOTES

<sup>1</sup>The following are among the key literature on drug lag: S. Peltzman, *Regulation of Pharmaceutical Innovation* (1974); W. M. Wardell & L. Lasagna, *Regulation and Drug Development* (1975); H. G. Grabowski & J. M. Vernon, *The Regulation of Pharmaceuticals* (1983).

<sup>2</sup>Grabowski & Vernon, *supra* at 4 (1983).

<sup>3</sup>*Id.*

<sup>4</sup>S. Peltzman, *supra* n. 1, at 18 (1974).

<sup>5</sup>Pharmaceutical Manufacturers Association, *New Drug Approvals in 1989* at 1.

<sup>6</sup>Grabowski & Vernon, *supra* n. 1, at 30-33.

<sup>7</sup>Wardell, May & Trimble, "New Drug Development By United States Pharmaceutical Firms," 32 *Clin. Pharm. & Therapeutics* 407, 415 (1982). The decline was found in "self-originated" new drugs—that is, compounds being tested by the US firms that had developed them. The rate of testing subsequently increased in the 1980s.

<sup>8</sup>Peltzman, *supra* n. 1, at 18.

<sup>9</sup>Wardell & Lasagna, *supra* n. 1, at 58-59.

<sup>10</sup>Katlin, Mattison, Northington & Lasagna, "The Drug Lag: An Update of New Drug Introductions in the United States and in the United Kingdom, 1977 Through 1987," 46 *Clin. Pharm. & Therapeutics* 121 (1989).

<sup>11</sup>*Id.* at 135.

<sup>12</sup>These are generally referred to as Type I and Type II errors. See, e.g., Grabowski & Vernon, *supra* n. 1, at 9-13.

<sup>13</sup>As quoted in Grabowski & Vernon, *supra* n. 1, at 5.

<sup>14</sup>Dr. Michael Murphy of Hoechst-Roussel, as quoted in "Wichita Falls Calls the FDA", *Wall Street Journal*, April 29, 1988, at 22.

<sup>15</sup>"Cancer Institute: AIDS drugs unduly delayed," *Chicago Tribune*, January 5, 1989, at 4.

<sup>16</sup>Kennedy, "A Calm Look at 'Drug Lag'," 239 *JAMA* 423, 425 (1978).

<sup>17</sup>Wardell, "A Close Inspection of the 'Calm Look'," 239 *JAMA* 2004, 2010 (1978).

<sup>18</sup>See, e.g., "Drug Approval Hit—Congressional Panel Issues Scathing Report On Licensing of Drug Implicated in 30 Deaths," *Washington Post-Health*, July 21, 1987, at 6.

<sup>19</sup>H. Schwartz, "A 'Miracle' Drug That Languished Among the Worms," *Wall Street Journal*, July 18, 1989, at A22.

<sup>20</sup>See e.g., "Plan to Speed Approval of Test Drugs Pits Small Companies Against Big Ones," *Wall Street Journal*, April 3, 1987, at 33.

<sup>21</sup>Wardell, *supra* n. 17.

<sup>22</sup>Some typical headlines were "U.S. Halves Dosage For AIDS Drug" (*New York Times*) and "AZT Anti-AIDS Medication Cut in Half By FDA" (*Washington Times*). The opening line in another newspaper's story began "FDA today halved the recommend dose..." (*Washington Post*). The *Wall Street Journal's* article was a notable exception, headlined "FDA Lets Wellcome Cut Dosage..." (The stories all appeared in the January 17, 1990, issues of the above newspapers.)

<sup>23</sup>GAO, *FDA Drug Review—Post Approval Risks*, 1976-85, April 1990 (GAO/PEMD-90-15).

<sup>24</sup>See GAO, *FDA Drug Approval—A Lengthy Process That Delays The Availability of Important New Drugs*, May 1980 (HRD-80-64).

<sup>25</sup>G. D. Searle & Co., Press Release, December 27, 1988.

<sup>26</sup>Thrombolytic therapy might eventually go beyond hospital use, and be administered by paramedics and others in victims' homes and workplaces. *Circulation* 474 (1987). It would thus begin to reach the 400,000 heart attack victims who die annually before reaching a hospital. To the extent that FDA's delayed approval impeded this extension of thrombolysis, its effect in terms of lives lost is even greater.

The drug lag computation for streptokinase is slightly complicated by the fact that,

to a very limited extent, the drug was available for thrombolytic heart attack therapy prior to 1987. In 1982 FDA approved the drug for direct injection into coronary arteries, a procedure that is for more difficult than intravenous administration and that was used very infrequently.

<sup>27</sup>TPA and PDQ," 237 *Science* 341 (July 24, 1987).

<sup>28</sup>A recent study casts some doubt on whether TPA is more effective than streptokinase, especially when these agents are used in conjunction with heparin. See, e.g., "Old Heart Drug Works as Well as Costly TPA in Study," *Wall Street Journal*, March 9, 1990, at B1. The current lack of any medical consensus on this issue illustrates the folly of leaving its resolution to a federal agency.

<sup>29</sup>Administrative Conference of the US, Colloquy on the FDA Drug Approval Process in the AIDS Era (July 25, 1989), Transcript at 68, 71.

<sup>30</sup>See, e.g., A. Sinclair, *Era of Excess: Social History of the Prohibition Movement* 201 (1964).

<sup>31</sup>D. Gieringer, "Compassion vs. Control: FDA Investigational Drug Regulation 24," *Cato Policy Analysis* (May 20, 1986). The author proposes the sale of unproven drugs using a scale of safety and efficacy ratings.